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09/027,654	02/23/1998	JEFFREY KENNETH HORTON	28911/34561	3465

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EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/027,654	HORTON, JEFFREY KENNETH	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 6/17/02 in Paper No. 21 are acknowledged and have been entered. Claim 15 has been cancelled. Claims 1 and 18 have been amended. Accordingly, claims 1-2, 4-14, and 16-21 are pending and are under examination.

Rejection Withdrawn

2. The rejections of claim 15 under 35 U.S.C. 112 and 102 are now moot in light of Applicant's cancellation of the claim.

3. In light of Applicant's amendment and arguments, the rejection of claims 14 and 20 under 35 U.S.C. 102(e) as being anticipated by Lundin (US 5,705,345), is hereby, withdrawn.

Rejection Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2, 4-13, 16-19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 step ii), as amended, is redundant and confusing because it lacks clear antecedent support in reciting, "mixing ... with a specific binding reagent comprising ... to perform a specific binding assay by forming a reaction mixture...". Perhaps Applicant should recite, "mixing and reacting the lysed cellular sample with a specific binding assay reagent comprising a specific binding partner of the analyte and a tracer to perform a specific binding assay; thus forming specific binding partner - analyte complexes;"

Claim 17 is indefinite in reciting, "the assay reagents comprise a tracer" because it fails to further limit the limitation recited in amended claim 1. See also claim 14.

Claim 14 remains indefinite in reciting, " which method further comprises the step of separating bound tracer from unbound tracer" since it recites a method step in a kit claim. It appears that the method step should belong with claim 17, instead.

Claim 18 is vague and indefinite in reciting, "assay reagent comprises a label for detection" because it is unclear as to how the label in the instant claim relates to the "tracer" in claim 1 from which it depends.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-2, 4-5, 8, 10, 14, 16-18, and 20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Khanna (US 5,032,503) for reason of record or as follows.

Khanna et al. disclose a specific binding assay for determining the presence of analyte in a cell sample (whole blood) (see column 3, lines 11-20 and column 2, lines 50-54). Specifically, Khanna et al. disclose mixing the cell sample with a detergent (surfactant), specific binding partners for the analyte (anti-analyte antibody, enzyme-analyte conjugate), and cyclodextrin to initiate complex formation, whereby the presence of analyte and specific binding partner reaction is indicative of the presence of the analyte in the sample. Khanna et al. specifically disclose that cyclodextrin is not added to the detergent and specific binding partners for the analyte, prior to the addition of the sample; thus, cyclodextrin is added to a reaction mixture initially formed by the combination of the cell sample, the detergent, and the specific binding partners for the analyte (see column 5, lines 12-32). Khanna et al. also disclose labeling the specific binding partners, i.e. fluorescer, enzyme (see column 3, lines 21-40). Khanna et al. disclose using dodecyltrimethylammonium bromide as a detergent for the assay (see column 3, line 41 to column 4, line 4). Specifically, Khanna et al. disclose using cyclodextrin in a sufficient amount to neutralize the detergent and allow complex formation between the specific binding partners. Cyclodextrin concentrations including an amount of 1-5% of the reaction mixture is set forth in column 4, lines 37-58. Khanna et al. also disclose a kit suitable for diagnostic immunoassay of the analytes comprising

a detergent, cyclodextrin, specific binding partners, assay buffers, drying agents, and excepients, i.e. to remove materials as in unbound tracers (see column 7, lines 37-60).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 7, 11-13, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna (US 5,032,503) in view of Brown et al. (US 5,739,001) for reason of record.

Khanna et al. has been discussed supra. Khanna et al. differ from the instant invention in failing to disclose that the cells are cultured, lysed, and assayed in a single vessel and in the presence of the culture medium. Khanna et al. further differ in failing to disclose assaying for cyclic AMP and separating bound from unbound tracers.

Brown et al. disclose a specific binding assay (cell-based assay) for determining the presence of cell-related analyte in a cell sample. Specifically, Brown et al. disclose mixing the cell sample (whole blood) with a lysis reagent to lyse red blood cells in the sample. Brown et al. also disclose mixing the lysed cellular sample with a specific binding partner for the analyte, i.e. anti-LTC_4 antibody for Leukotriene C_4, in order to form analyte-specific binding partner complexes whereby the presence of analyte and specific binding partner complexes is indicative of the presence of the analyte in the

sample. See Example 2 and column 3, lines 18-42. Other analytes that can be detected using this method include adenosine-3', 5'- cyclic monophosphate (cyclic AMP) and cytokines, i.e. interleukin-6 (see column 4, lines 59-64). Brown et al. disclose that the assay is a homogeneous assay that is performed in a single reaction vessel (cells are not attached to solid phase for assay) (see column 4, lines 5-12 and lines 38-56). The cells are cultured, lysed, and assayed in the same vessel; thus, eliminating the need for a separate culturing step (see column 3, line 66 to column 4, line 1). The specific binding partners can be immune type, i.e. antibody or non-immune type, i.e. biotin/avidin (see column 5, lines 12-38). Brown et al. also disclose labeling the specific binding partner with a tracer or label, i.e. ^{3}H and ^{125}I (see column 6, lines 5-16).

One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Brown in culturing, lysing, and assaying for intracellular analyte such as cyclic AMP in a single reaction vessel, into the cell-based immunodiagnostic assay taught by Khanna because Brown's method provides a capability to detect both intracellular and cell-surface analytes and their functions, from samples grown in a cell culture medium in a single reaction vessel; thus, eliminating the need for a separate "culturing step" that would have been otherwise required.

7. Claims 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna (US 5,032,503) in view of Cook (2) (WO 94/26413) for reason of record.

Khanna et al. have been discussed supra. Khanna et al. differ from the instant invention in failing to teach a multiwell plate. Khanna et al. further differ in failing to teach scintillation proximity assay.

Cook (2) discloses an apparatus and method for studying cellular processes using scintillation proximity assay. The apparatus comprises a vessel having a base with a scintillant substance and which is adapted for attachment and growth of cells (see Abstract). Cook (2) further discloses a multiwell plate comprising an array of wells held in fixed relationship to one another wherein each well is a vessel (see page 10, first full paragraph). The scintillant substance includes aromatic hydrocarbons which emit light used for detection. The method of studying cellular processes includes introducing into the vessel a sample of cells labeled with a radioisotope emitting electrons, and using detection means to observe scintillation caused by radioactive decay so as to study the cellular process (see page 10, second full paragraph). The multiwell plate can take various formats for the purpose of culturing cells using standard cell culture media and growing cells in a sterile environment at 37 C in a 95 % humidified air and 5% CO2 incubator as well as studying cellular biochemical processes in living cells (page 14, second and third full paragraphs and page 15, second full paragraph). Cook (2) disclose that the surface of wells or vessels in the microwell plate requires modification in order to be adapted for the attachment and/or growth of cells. Cook (2) disclose that a considerable advantage of the scintillation proximity assay is that it does not require separation of bound and molecular species from free, thereby minimizing handling of potentially hazardous substances (see page 7, second full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the scintillation proximity multiwell assay system having an array of reaction vessels as taught by Cook (2) into the cell-based immunodiagnostic assay taught by Khanna because the system taught by Cook (2) provides advantage in minimal handling of materials in high-throughput immunoassay testing of a plurality of live culture cells, in order to screen for cellular analytes, functions, and processes. One of ordinary skill in the art would have been motivated to incorporate the derivatized multiwell system of Cook (2) into the method of Khanna because of the high throughput capacity achieved in simultaneously assaying for identification of a wide variety of biochemical and cellular analytes.

8. Claim 21 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna (US 5,032,503) in view of Edmonds (US 6,159,750) for reason of record.

Khanna et al. has been discussed supra. Khanna et al. differ from the instant invention in failing to teach that the specific binding assay is fluorescence polarization assay.

Edmonds discloses a specific binding assay for the detection of analytes, i.e. T4 hormone and Free Estriol, wherein reagents, i.e. antibodies or specific binding partners and labels, are mixed with the sample containing the analyte and are caused to react. Edmonds discloses using fluorescence polarization assay to detect and measure the concentration of the analyte in the sample. See Abstract, Example 2, and Example 4.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to detect the polarization characteristics of the specific binding assay taught by Khanna using fluorescence polarization assay as taught by Edmonds because Khanna is generic with respect to the type of detection used in detecting the presence and amount of the analyte and Edmonds specifically taught that fluorescence polarization immunoassay is a common and conventional method of analyzing samples for the presence of analyte of interest.

Response to Arguments

9. Applicant's arguments filed 6/17/02 have been fully considered but they are not persuasive.

A) Applicant argues that Khanna et al. fail to teach or fairly suggest the teaching of the claimed invention because Khanna et al. does not disclose mixing a sample of cells with a cell lysis reagent (e.g. detergent), as a pretreatment method, but rather use of a surfactant to inhibit complex formation between complementary members of a specific binding pair. According to Applicant, no pre-treatment step of the sample is performed in Khanna et al.

In response, Khanna et al. indeed, teach each and every element taught by the claimed invention. Specifically, Khanna et al. disclose a specific binding assay method for determining the presence of analyte in a cell sample, i.e. whole blood, by mixing the cell sample with dodecyltrimethylammonium bromide as a detergent and also specific binding partners for the analyte; thereafter, cyclodextrin is added to the reaction mixture

initially formed by the combination of the cell sample, the detergent, and the specific binding partners for the analyte, in order to neutralize, i.e. sequester, the effects of the detergent (see column 5, lines 12-32 and column 3, lines 49-55). Khanna et al. also disclose including a label for the specific binding partners, i.e. fluorescer, enzyme for detection of the complexes formed (see column 3, lines 21-40). Alternatively, claim 1 recites a specific binding assay that "comprises" each of the elements taught by Khanna et al. and does not exclude that the detergent, i.e. dodecyltrimethylammonium bromide (used by Khanna et al.) is used to "pretreat" the sample at specific concentrations effective to specifically cause the cells in the sample to lyse. Further, there is no requirement in the claim to distinctly define that the analyte that is detected is intracellular and/or extracellular analyte that is released from lysis of the cells; only that presence of analyte (specific for the specific binding partner in the assay reagent) is detected; thus encompassing the teaching of Khanna et al. While Khanna et al. is silent in disclosing that the cells in the whole blood sample are caused to be lyzed by dodecyltrimethylammonium bromide as detergent, albeit used to inhibit binding or induce dissociation between certain binding partners; detergents, including dodecyltrimethylammonium bromide, are nevertheless capable of lysing, are known to lyse, and have been used to lyse, cells in a cellular sample. Absent evidence to the contrary, the cells in the whole blood sample in the method of Khanna et al. would have been lysed by dodecyltrimethylammonium bromide. Accordingly, there is no patentable distinction seen between the rejected claims and Khanna et al.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

B) Applicant argues that Brown et al. does not make up for the deficiencies of Khanna et al. and the combination of Khanna et al. with Brown et al. fails to suggest the teaching of the claimed invention. According to Applicant, the assay disclosed in Brown involves cell lysis by a detergent (Triton X-100) without the sequestration by cyclodextrin and is silent with the adverse effects of the lysis reagent upon the binding reaction between the analyte and its specific binding partner.

In response to Applicant's argument that Brown et al. fail to disclose of the lysis reagent (Triton X-100) having *adverse effects upon the binding reaction between the analyte and its specific binding partner*, it is noted that such feature upon which Applicant relies for argument, is not recited in the rejected claims. Additionally, the teaching of Brown et al. was incorporated with the teaching of Khanna et al. only for the disclosure of a homogeneous cell-based specific binding assay that is performed in a single reaction vessel in column 4, lines 5-12 and lines 38-56, wherein the cells can be, and are cultured, lysed, and assayed in a same vessel; thus, eliminating the need for a separate culturing step (see column 3, line 66 to column 4, line 1). Brown et al. specifically disclose lysing the cellular sample in order to effect detection of both

intracellular and extracellular analytes such as adenosine-3', 5'- cyclic monophosphate (cyclic AMP) and cytokines, i.e. interleukin-6 (see column 4, lines 59-64). One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Brown in culturing and lysing cellular samples for assaying the presence of intracellular analyte such as cyclic AMP in a single reaction vessel, into the cell-based immunodiagnostic assay taught by Khanna because Brown's method provides a capability to perform multiple tasks in a single vessel; thus, eliminating the need for a separate "culturing step" that would have been otherwise required.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

C) Applicant argues that Cook does not make up for the deficiencies of Khanna et al. and the combination of Khanna et al. with Cook fails to suggest the teaching of the claimed invention. According to Applicant, an essential feature of the claimed invention is the ability to lyse cells within the wells and then utilize cyclodextrin to neutralize the cell lysis reagent whereas Cook only teaches a multiwell system utilizing a scintillant.

In response, the teaching of Cook was incorporated with the teaching of Khanna et al. supra, only for the disclosure of a multiwell plate comprising an array of wells held

in fixed relationship to one another wherein each well is a vessel in page 10, first full paragraph, for use in studying cellular processes in scintillation proximity assays. The multiwell plate can take various formats for the purpose of culturing cells using standard cell culture media and growing cells in a sterile environment at 37 C in a 95 % humidified air and 5% CO2 incubator. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the scintillation proximity multiwell assay system having an array of reaction vessels as taught by Cook (2) into the cell-based immunodiagnostic assay taught by Khanna because the system taught by Cook (2) provides advantage in minimal handling of materials in high-throughput immunoassay testing of a plurality of live culture cells, in order to screen for cellular analytes, functions, and processes.

In response to Applicant's argument that "pretreatment lysis method" is not taught or suggested, Khanna et al. upon which Cook is combined, is relied upon for the teaching of mixing the cell sample with detergent capable of lysing cells in cellular samples, assay reagent, and a neutralizing reagent for the detergent, and detecting analyte present in the sample, such as recited in the rejected claims.

D) Applicant argues that Edmonds does not make up for the deficiencies of Khanna et al. by failing to teach a "pretreatment lysing" step and failing to disclose applicability of the detection method to cell samples. Applicant therefore contends that the combination of Khanna et al. with Edmonds fails to suggest the teaching of the claimed invention.

In response, the teaching of Edwards was incorporated with the teaching of Khanna et al. supra, only for the disclosure of using fluorescence polarization for detection of specific binding assay measurement of the concentration of analyte in a sample. In as far as the "pretreatment lysis method", Khanna et al. upon which Edmonds is combined, is relied upon for the teaching of mixing the cell sample with detergent capable of lysing cells in cellular samples, assay reagent, and a neutralizing reagent for the detergent, and detecting analyte present in the sample, such as recited in the rejected claims.

In response to applicant's argument that the combination of Khanna et al. with Edmonds fail to show applicability of fluorescence polarization taught in detecting analyte in cellular samples, it is noted that this feature upon which applicant relies is not recited and intended in the rejected claim, since the analyte in the "cellular samples" in claim 1 are caused to be released from lysis of the cells in the sample. Therefore, fluorescence polarization in the rejected claims detect free soluble analyte, such as suggested by Edmonds.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

10. For reasons aforementioned, no claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gail Gabel
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9/23/02

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9/20/02